Early Journal Content on JSTOR, Free to Anyone in the World

This article is one of nearly 500,000 scholarly works digitized and made freely available to everyone in the world by JSTOR.

Known as the Early Journal Content, this set of works include research articles, news, letters, and other writings published in more than 200 of the oldest leading academic journals. The works date from the mid-seventeenth to the early twentieth centuries.

We encourage people to read and share the Early Journal Content openly and to tell others that this resource exists. People may post this content online or redistribute in any way for non-commercial purposes.

Read more about Early Journal Content at http://about.jstor.org/participate-jstor/individuals/early-journal-content.

JSTOR is a digital library of academic journals, books, and primary source objects. JSTOR helps people discover, use, and build upon a wide range of content through a powerful research and teaching platform, and preserves this content for future generations. JSTOR is part of ITHAKA, a not-for-profit organization that also includes Ithaka S+R and Portico. For more information about JSTOR, please contact support@jstor.org.

SEROLOGICAL REACTIONS AS A PROBABLE CAUSE OF VARIATIONS

PROFESSOR M. F. GUYER

UNIVERSITY OF WISCONSIN

WITH an insight that has never been surpassed even to this day Claude Bernard,[1] more than forty years ago, remarked that " Organic synthesis, generation, regeneration, maintenance, and healing of wounds, are different aspects of an identical phenomenon," the phenomenon alluded to being the constructive activity manifested in ordinary nutritive processes. In a recent thoughtful paper, R. S. Lillie[2] reiterates and expands this point of view. That synthetic metabolism constitutes the very essence of embryonic development and therefore of the expression of heredity, scarcely admits of a doubt. To-day it is a truism to say that the visible " characters " we deal with in heredity are but the effects—by-products as it were—of far-reaching metabolic reactions. And since the metabolism of the actual living protoplasm centers, if not exclusively, at least principally, in the proteins, the problems of metabolism, growth, reproduction and heredity become largely the problem of why and how a given kind of living protoplasm builds up proteins of its own specific type.

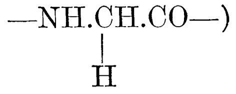
The molecules of the ordinary native proteins are, as is well known, huge polymeric structures of extremely complex constitution. By appropriate chemical treatment they may be broken down into successively smaller and smaller units, each of which, however, still responds to the ordinary qualitative tests for proteins. There finally comes a point below which further reduction of the molecule results in the loss of the distinctive protein reaction, and the outcome is a series of ultimate characteristic units, the amino-acids. Thus native proteins seem to be built up of two different categories of units: first, combinations of various amino-acids which constitute the simplest protein blocks; and second, the combination of these into the much larger molecules characteristic of the native proteins.

---

[1] "Leçons sur les phénomènes de la vie," Vol. II, p. 517.

[2] *Biol. Bull.*, XXXIV, 2, 1918.

In the process of digestion different proteins are broken down into their amino-acid units and these are then rebuilt into the tissue-proteins of the living organism, each tissue selecting such amino-acids as are required to reconstruct its own peculiar complex. That is, the architecture of the new proteins into which the individual building units are regrouped is determined by the specific constitution of the tissue-proteins themselves. In different proteins the different amino-acids may exist in very different ratios, and certain of them necessary for the metabolic repair of protoplasm may be lacking in some, such as gelatin, but the amino-acids in any particular protein are constant in nature and proportion and each probably has a definite position in the molecule. While kinds and proportions of amino-acid units determine in large measure the characteristics of individual proteins, it may well be that configurational differences in molecules of the same chemical composition are responsible for the specificities of corresponding proteins in related species of animals. One estimate, for instance, assigns to the serum-albumin molecule alone the capability of having as many as ten thousand million stereoisomers. One may perhaps picture mentally, in a much simplified form, the simplest protein molecule as a main chain or ring, of which the representative links are amino-acid "nuclei." Moreover, to each such link

(*e.g.*, in simplest form, 

$\text{—NH.}\underset{\displaystyle\overset{|}{\text{H}}}{\text{C}}\text{H.CO—}$)

a side-chain, differing in constitution in different cases, is attached or is attachable by replacement of a hydrogen atom.

It is, then, with such complex molecular configurations that we have to do as a chemical basis for the phenomena of life; and in them, as I have stated elsewhere,[3] we have "ample basis for that peculiar handing on of metabolic energies already established which we term *heredity.*"

Although habitually when speaking of heredity we think of the multifarious "characters" displayed by the adult organism as the things inherited, and strive to picture in our minds how they are represented in the germ, it is clear, in the light of modern genetics, embryology and cytology, that what actually happens is a reduplication generation after generation of germinal protoplasm. That is, the proteins already present in the germ-cell not only determine what will be built up in growth, but also the composition of that overgrowth which, as a detached individual, constitutes the physical basis of inheritance. If the initial protoplasmic substance is chemically specific then inevitably the anatomical and physiological complexities which arise out of it must likewise be specific.

---

[3] AMER. NAT., XLV, May, 1911.

Before we can grapple with the problem of the possible induction of changes in this fundamental mechanism through influences emanating from the body, we must consider some matters concerned with embryonic development and the fundamental chemical nature of the somatic cells.

As to how the constitution of the egg becomes transformed into that of the adult, the most consistent and reasonable hypothesis to date, in my opinion, is that proposed by Child, based on axial or metabolic gradients. A full exposition of his hypothesis must be sought in his books, " Individuality in Organisms " and " The Origin and Development of the Nervous System from a Physiological Viewpoint." I can sketch only such aspects of it as pertain to my present subject. Starting with the universally accepted biological axiom that excitability followed by some degree of transmissibility is a fundamental property of all living matter, Child believes, as I understand him, that the establishment of polarity in the fundamental organismic proteins of the germ-cell is the beginning of development. The eggs of many species already show polarity (animal and vegetal pole) at the time of ovulation; in other forms polarity is not established until later. In the former case the polarity may have been determined in earlier cell-generations by extrinsic factors or it may be due to the original position of the ovum in the ovary with reference to the nutritive stream. Yolk apparently accumulates in the region of least oxidation and thus marks the vegetal pole. In the second type of egg, polarity, at first lacking, is soon established because differential environmental exposure (difference in oxygen supply, light, contact, general surface exposure, or other external factor or factors) causes one region to have the greatest metabolic activity. As does any stimulated part with reference to a resting part (muscle, nerve, etc.), this point of heightened activity sets the pace, as it were, for the other parts. Thus an excitation gradient is established which Child terms an *axial gradient.* Since the excitation initiates transmission—changes and thereby determines what shall happen at successive levels along the path of transmission, the region of highest excitation dominating and controlling the rest, the axis in question may also be called a *metabolic gradient.* In this way a physiological unity is established and maintained by bringing the different regions within range of the gradient into definite physiological relations.

Since the chief source of energy in protoplasm is oxidation, and inasmuch as many different tests have shown that the rate of oxidation gradually diminishes along the gradient from the region of highest activity, Child infers that differences in oxygen supply play a very important part in the local metabolic differences which arise. In any event, a differential axis of activity arises in the egg as the result of differences in environmental conditions (either before or after ovulation) and determines the axiate pattern of the developing organism. In such a complex system of chemical and physical activities, where unquestionably many associated simultaneous reactions and interactions are going on, different rates or conditions of reaction in different regions must result in unlike end-products. Thus, at different levels of a gradient which was quantitative in origin, *qualitative* differences arise. For once a gradient is established, any one of several purely quantitative changes in the system, such as increased oxidation which acts differentially on substances at a given point, changes in temperature, in water content, or in colloidal state, or changes in the concentration of the reacting substances, may alter certain component factors of a given region more than it does the corresponding factors in other regions, with the result that out of the same initial constituents the respective organ- or tissue-stuffs that characterize the organism are gradually built up. For example, as Child points out, in a region of rapid oxidation certain substances might be entirely oxidized as rapidly as they are formed, while in a region of slower oxidation they might accumulate as part of the structure.

Bilateral organisms follow a law of antero-posterior development. Differential exposure having determined which region shall lead and having thus set the rate of activity of the successive regions, continuing differential relations of the environment maintain the various levels of the gradient, under the domination of the head-end, at their respective rates of activity. While this is the normal course of development, it may be greatly altered by experimental methods; the original gradient, particularly in lower organisms, may be obliterated and a new one engendered. The latter under certain conditions may even be made to arise at right angles to the original axis. Change of gradient may be readily observed, for example, in the regulatory development of isolated pieces of many planarians. Moreover, the remarkable capacity for self-differentiation possessed by isolated parts taken at different levels of the body in such forms, shows that positional relations of the constituents of the regenerating mass, rather than cellular specificity, determine what structures shall arise in a given location.

Since many species, including representatives from all the chief phyla of animals, show differential susceptibility at some stage of their development, when subjected to the action of various external agents such as alcohol, anæsthetics or potassium cyanide, these agents may be used to bring about shifts of gradient, under-development or over-development of certain parts, or a remodelling of the organism or of various regions of it. Inasmuch as any one of several agents may bring about the same result, it is manifest, again, that quantitative external conditions are the factors which initiate and thereby determine the fundamental orientations and specializations of the parts of an organism.

As development progresses in the more complex organisms, again through differential stimulation, secondary or "symmetry" gradients may also become established. For example, each limb region of a vertebrate becomes a subordinate system with its own internal correlations.

In organisms with radial symmetry, special centers of growth occur, and only at a certain distance from a given center can another arise.

After differences in protoplasmic constitution have arisen at different levels of the gradient, a system of chemical or transportative correlation probably begins to operate, and out of it all finally comes the various supportive and mechanical tissues, vascular tissues, tissues of excretion and secretion, nervous tissues, etc., which constitute the underlying mechanisms of correlation and integration in the finished organism.

The hypothesis says little of chromosomes, or of genes, for its objective differs somewhat from that of the geneticist, but it in no wise denies the existence of such entities. Child argues, however, that since each cell of the body is a descendant of the original zygote and therefore presumably possesses the full complement of chromosomes of that zygote, something other than the nuclear pattern *per se* must be responsible for the fact that cells become different in different parts of the body. And this something, he would say, is the metabolic gradient initiated by differential excitation, since the very establishment of such a gradient means the concomitant establishment of local differences along its path. As he says, " if all the cells are originally alike they cannot of themselves become different." The specific character of the differentiation, the kind of organ or organism produced, he reiterates, is determined " by the specific inherited constitution of the protoplasm."

So much for Child's hypothesis of axial or metabolic gradients, in its bearings on embryogeny and differentiation. I have reviewed it at some length because it shows more clearly than any other theory of development with which I am acquainted that there is no necessity for believing that as cells become specialized they lose part of their original constituents. Due to local conditions, structural modifications and special activities have appeared, but these are changes rung on what is fundamentally the same type of protoplasm in every cell. In higher organisms, in some cells possibly irreversible changes have occurred—the cell may be incapable of dedifferentiation —but nothing constitutional, call it gene or what you will, has necessarily been lost from the cell. The inheritance complex of the germ is like goods in the piece; it is only as development progresses that the garment becomes specified; but above all, be it remembered that the finished garment is of the same fundamental constitution as the goods in the piece.

It is a commonplace of experimental embryology and experimental morphology, in fact, that the same initial materials may yield very different end-products in different environments. The phenomena of heteromorphosis, metaplasia, regeneration and regulation all attest this. Blastomeres originally directed toward becoming one part of an organism may be switched about to become another part; tissues originally subserving one function may be turned to other uses; ectodermal cells which by no possible chance could have been predestined to form crystalline lens will, nevertheless, form a lens similar to that of the normal eye if stimulated by a transplanted optic cup. Or, if the lens is removed from the eye of a salamander, a new lens may develop from the edge of the old iris, a part from which the lens never normally develops in the embryo. In short, it is a well-established fact in many organisms that cells occupied with the specializations of one part of the individual still retain the potentialities which would fit them to the functions of some different part, and may, in fact, under experimental conditions be made to redifferentiate into the structures of another part. Such facts, together with the exactitude of chromosome distribution in mitosis, indicate clearly that many, possibly all, cells of an organism retain the hereditary tendencies that existed in the original zygote. Because of limitations due to its location in the organism, however, a given cell realizes only a small proportion of its inherent possibilities. And after all, this is no more remarkable than the fact that the genes of recessive characters may slumber indefinitely in germ and soma, generation after generation, until conditions suitable for their expression as characters occur.

But now, regarding heredity as in its simplest expression merely the passing on of metabolic activities already established, and conceding that the distinctive structural effects and functions which characterize the respective tissues are probably the outcome of unequal activities among the same kinds of fundamental protoplasmic constituents in differing local environments, the question of prime importance to the student of evolution is how the properties of these constituents have come to be changed from what they were initially, how they may be altered in the future—in short, the question of the nature and origin of variations. For whatever we may believe about the degree of preformation which exists to-day in the mechanism of heredity, it is absurd to assume that in the simpler primitive protoplasm from which modern forms have evolved there could have been genes of the characteristics of all the organisms now in existence. Whatever individual development may be, we must assume that racial evolution was epigenetic. While doubtless in a sense man lived potentially in some primitive protozoan-like creature, actual material antecedents of his existing attributes were no more present in this ancestral creature than specific determiners for the oceans, continents and topographical features of the world to-day were present in the original nebula which preceded our solar system. The great central problem of evolution is just this very one of how the determinative accumulations which exist in germ-cells to-day have been incorporated step by step into this erstwhile primitive protoplasm. Certain possibilities have become realities and concomitantly as a basis of this reality the old mechanism has in part been altered, or a new mechanism has come into being which persists as a part of the established constitution of the germ-cell.

Before entering upon a discussion of whether or not any of the remarkable serological activities which have come to light in recent years may be possible or probable sources of germinal modifications, we must recall briefly the general nature of immunologic reactions. As you know, foreign proteins of either plant or animal origin when injected directly or indirectly into the circulation of an animal will engender antagonistic or neutralizing substances to which the general name of *antibodies* is applied. Thus the toxins of bacteria incite the production of *antitoxins;* the bacteria themselves lead to the production of bacterial immobilizers or solvents termed *bacteriolysins,* or sometimes to agglutinating substances termed *agglutinins* which clump bacteria of the species used in their production, if the two are brought together in the blood-serum of the animal into which the bacteria were originally introduced. Likewise a tissue of one kind of animal injected into the circulation of another induces the formation of antibodies of various kinds such as *precipitins* which form a precipitate when the blood-serum of the treated animal and an extract of the special tissue used are brought together in vitro; or other antibodies termed *cytotoxins* or *cytolysins* which possess a specific toxic or solvent action for the kind of protein used in their production. The alien substance employed to produce antibodies is commonly called the *antigen.*

In this connection, the phenomenon of anaphylaxis should perhaps also be mentioned. Anaphylaxis is a name given by Richet to designate a highly supersensitive state which, after a period of incubation, an animal develops toward certain protein substances that were practically harmless on first injection. Sometimes, particularly in guinea pigs, death results. The sensitizing dose for the production of anaphylaxis may be very small; one millionth cubic centimeter of horse-serum, for example, has been known to render guinea pigs sensitive. The reaction is specific; for instance, an animal sensitized to sheep-serum, though reacting violently to this antigen, displays little or no hypersusceptibility to other sera.

In the main all of the immunological reactions show a considerable degree of specificity; the antibody will react fully only with the particular kind of protein used as antigen. The specificity is not absolute, however; a milder reaction may be obtained with homologous proteins of related species, the extent of the reaction being determined by the nearness of relationship of the species to that from which the original antigen was obtained. Similarly with bacteria, the reaction is in the main specific, although so-called group-reactions may appear. The serum of an animal immunized against typhoid, for example, may not only agglutinate *Bacillus typhosus* but may also show this reaction in a less degree with such related forms as the colon bacillus. Thus, irrespective of whether the antigen consists of bacteria or of other protein materials, there is a gradational specificity of reactions which apparently corresponds to taxonomic relationships.

An even more delicate biochemical measure of kinship than the known immunological reactions has apparently been established through the extensive researches of Leo Loeb[4] and his associates on transplanted tissues. In numerous of his papers Loeb has called attention to the remarkable power of transplanted tissues to indicate different degrees of even close individual relationship, such as the individual to itself, to a brother or sister, to a parent, to a more distantly related individual of the same species, or to an individual of a different species. Particularly the lymphocytes of the host serve as a delicate indicator of such relationships.

Loeb assumes that a specific chemical group which he designates as *individuality-differential* is common to all the tissues of an individual and that in virtue of this characteristic each creature differs from the others of the same species. The individuality-differential of a transplant (except in autotransplantation), since it is not adapted to its new environment, assumes injurious properties, probably by engendering toxins. The relative strengths of these are determined by the degree of relationship that exists between the source of the transplant and the host. In the circulating fluids of a given individual, he believes that there are "autosubstances" which exercise important regulative functions, such, for example, as keeping the vascular supply of the various tissues at an optimum, or holding in check lymphocytes and invasive fibroblasts which when inadequately restrained, as in old age, become destructive agents. In one place he speaks of their stimulating effects and he regards them as responsible directly or indirectly for the marked vascular reaction called forth by autotransplants.

In sexual reproduction, obviously two different "individuality-differentials" must combine to form the new individuality-differentials of the offspring. These, Loeb finds, are of varying degrees of intermediacy. This intermediacy is continued into the next generation. What is of much interest from the standpoint of our quest of a possible connection between reaction-products of the body and alterations of the germ is the fact that he feels constrained to link up his serumal phenomena with the chromosomes. Thus, he says, "The chemical individuality-character of the chromosomes should lead to analogous chemical differences consisting perhaps in the formation of chemical side-chains attached to proteins; they should be present primarily in cell-proteins and secondarily in the proteins of the body-fluids. . . . These side-chains must be identical in all the proteins of the same individual and differ in the case of different individuals."

---

[4] AMER. NAT., LIV, 1920.

Another great group of influences which extend to the furthermost reaches of the body and profoundly affect the entire organism in development and in maturity—those emanating from the various endocrine structures—I have barely time to mention. They must be kept in mind, however, when we attempt to picture the ebb and flow of chemical influence which is indispensable to the maintenance of general physiological equilibrium, including that of the gonads no less than of the other body structures.

You may feel that in reviewing the nature of the protein molecule, the behavior of the proteins of the cells in morphogenesis, the gradational specificities of the immunological reactions, the relationships which exist between host and transplant, and in reminding you of the intricate functions of the endocrines, I have wandered far afield into irrelevant byways, but I hasten to assert that these phenomena are not as unrelated as might appear at first sight; they are but different aspects of the great salient fact of organismic unity, whether it be a matter of chemical constitution, taxonomic relationship or physiologic response.

And now I wish to raise the question of whether or not in the light of the foregoing facts it is irrational to believe that in all probability a thread of chemical identity persists between the chemical constituents of the germ and the chemical substratum of the tissue-cells. The nuclei of the various tissue-cells differ little in appearance from the nuclei of the germ-cells, and inasmuch as the new germinal and somatic cells descend alike directly from a common source, presumably bearing in their chromosomes samples of all the chromosomal components of the original zygote, is it unreasonable to suppose that if changes come to pass which can affect certain constituents of tissue-cells, this influence, if borne in the circulating fluids of the body, could also affect the homologous constituents of the germ-cells? Personally, I think that such a hypothesis is not unreasonable. But is there even the least bit of evidence on this point? I believe that there is. I feel that in the transmission of eye-defects secured by Dr. E. A. Smith and myself in fetal rabbits by means of serum immunized against rabbit crystalline lens, we have a bona fide case of such parallel influences. Since I have already presented the facts before this Society and inasmuch as the details are available in printed form,[5] I need not repeat them now. It is sufficient to recall to you that we secured a fowl-serum immunized against rabbit crystalline lens which when injected into pregnant rabbits penetrated the placenta and occasionally attacked the lens of the fetal young, the outcome being marked eye-anomalies in such young. Since, once produced, the defects were transmitted to successive generations through both male and female lines, we interpreted our results to mean that the immune serum was not only specifically cytolytic for the newly forming lens-tissue of the fetus, but that it also attacked the representatives of such tissue—its genes, if you please—in at least some of the germ-cells of the fetus. If true, this must mean that there is some degree of constitutional identity, probably protein homology, between the mature substance of a tissue and its correlative in the germ. And in view of the fact that, basically, inheritance is mainly a question of the perpetuation of specific protein-complexes, and development, the result of differential reactions of these same fundamental constituents under differing conditions of environment, is this an unreasonable inference?

But does anything comparable to this occur in the ordinary course of animal existence? Do cytolysins or kindred substances which can modify or destroy both tissue-elements and their germinal correlatives ever occur in animals without being introduced by man? Do animals ever form such antibodies or other equally active substances against their own tissues? It is obvious, since tissues persist intact under conditions of normal physiological equilibrium, that they are not being subjected to such influences, or if they are, that they resist them. As a matter of fact, Römer,[6] using the complement-fixation technique, found that the serum of adult human beings may possess antibodies for their own lens proteins. It seems reasonable to suppose that if the tissues of an animal became injured or displaced in some way, or metabolically unbalanced, immunity reactions might be established against them. We have some evidence that such is the case. During the late war, for example, it was found that toxic reactions resembling anaphylactic shock often followed extensive injuries of the soft tissues. The matter can be tested experimentally. Because of their distinctive nature and the ease with which they may be isolated, I chose spermatozoa for such an experiment.[7] I found that a rabbit will build antibodies against its own spermatozoa when these are injected into its blood-stream; also, that rabbits injected with rabbit spermatozoa not only develop antibodies in their blood, but also have their own spermatozoa greatly weakened, a condition shown in vitro by their lessened resistance to antisera. This clearly shows that an animal can on occasion build antibodies against its own tissues; and since antibodies can apparently directly or indirectly affect germ-cells, it seems reasonable to suppose that such influences, especially if continued over a long period of time, might be one source of germinal variations.

---

[5] *Jour. Exp. Zool.*, 31, 2, 1920. AMER. NAT., LV, 1921. *Proc. Nat. Acad. Sci.*, 6, 3, 1920.

It is known from the experiments of Kuntz[8] and others that the blocking off of the ductus deferens of one testis may induce degeneration of the germinal epithelium, not only of that testis, but of the other as well. Inasmuch as the spermatozoa in the testis on the operated side must die and be resorbed, is it not probable that in this process spermatotoxins have been formed which have then attacked the living germ-cells of the other testis? Again, we are familiar with the fact that oculists frequently find it necessary to remove a severely injured eye to prevent the "sympathetic" degeneration of the other eye. I am told by competent oculists that the extension of the degenerative influence involves more than the atrophic effects which might result through direct nerve connections. Does it not seem probable that here, too, the disintegrative influence which comes to operate on the uninjured eye is cytotoxic or cytolytic in nature? And if it can operate on the tissues of the normal eye, why not on the corresponding protein constituents in the germ, the prototypes of those which were originally incited to form the ocular tissues?

---

[6] Zinsser: "Infection and Resistance."

[7] Paper in press, *Jour. Exp. Zool.*

[8] *Anat. Rec.*, 17, 4, 1919.

It may be, it probably is true that there is sufficient difference between these factors of the germinal protoplasm and those of the finished organ to render the former less susceptible to such agents. It is not improbable that even if some of the numerous germ-cells were affected many others might not be. But any new organism which sprang from such an affected germ would have its own germ-cells similarly modified, since these would all be derived from the same zygote. Even so, the defects might not be manifested in offspring because of the probability of dominance by the corresponding factors from their partner in fertilization.

The only way to settle the matter, of course, is through experiment. I know of no existing experimental evidence on this point. In my own laboratory, however, an investigator has an experiment in progress which I hope will ultimately throw some light on the matter.

There are many bits of evidence to show that an organism may react against the tissues of other individuals of its own species. Thus Bradley and Sansum,[9] employing anaphylactic reactions, found that guinea pigs injected with various guinea-pig tissues such as heart, liver, muscle, testicle, and kidney developed immunity reactions. Moreover, certain changes in the blood of the mother during pregnancy, apparently induced by cells or cell-products set free from the newly-forming placenta, seem to be of the nature of antibody formation. Then again Turck[10] has shown that products of the lung-tissue of the cat, autolysed under sterile conditions in *vitro,* pro-

[9] *Jour. Biol. Chem.,* Vol. 18, 1914.

[10] *Med. Rec.,* 1919, 95, pp. 719–21.

duced characteristic pulmonary lesions when injected into other cats. Similarly autolysed lung-tissue of other mammals had no effect on cats.

But, the question arises, in order to get parallel influences, in soma and germ, would there not have to be absolute identity between the two sets of proteins concerned? Before answering this question let us glance for a minute at two types of specificity which are recognized in serological reactions: namely, "species-specificity" and "organ-specificity." What the serologist means by species-specificity is the fact, shown through precipitin reactions, that blood immunized against one tissue of an alien species will react, although in a less degree, with extracts of the other tissues of that species. And that there may be a specificity of certain organ complexes which is independent of species is shown by the fact that an immune serum produced by using the crystalline lens of one species of animal yields a precipitin which reacts more or less with the lens proteins of even unrelated species. Similar results have been obtained with proteins derived from the testis, and confirmatory evidence of such organ-specificity has also been established by means of anaphylactic reactions. Such facts as these, together with those cited in the discussion of the gradational reactions of various immune sera according to the systematic relationships of animals, it seems to me, answer our question affirmatively; there need not be absolute identity between the proteins of the somatic cells and their correlatives in the germ-cells for immune sera engendered against the one to react also against the other. I raise the issue because it might be urged that such tissues of an organism as become so abnormal as to excite the production of antibodies are no longer sufficiently similar to the normal tissue-elements, and therefore to their germinal representatives, to make the antibodies effective against either normal somatic or germinal constituents.

It seems to me that all available facts indicate that the constitution of an organism, whether germ or soma, is not to be regarded as a congeries of cooperating, equipotent units, but rather as the outcome of interacting systems which differ in their orders of organization; systems which in themselves possess more fundamental and more supplementary or fluctuating components; chemical groups which represent the more constant features of organization coupled with subsidiary groups of more restricted significance. That is, there seem to be series of substances of like chemical constitution common to all the cells of an organism, possibly to even various groups of organisms, and superimposed upon these central or foundational constituents, probably as parts of the same molecules, are secondary systems, or possibly systems within systems, which modify the main configurations in various ways.

This conception certainly squares with the fact that degrees of specificity paralleling the kinships of animals may be shown by immune sera. It harmonizes with what we know of the architecture of the native proteins as well as with our whole scheme of natural biological taxonomy in which we find certain fundamental stable features representing a broad series of organisms, and less and less inclusive characteristics which grade down to the minor differences that separate species, varieties and individuals. Nor is it incompatible with what we know of chromosomes and genes. The very fact that heritable grades of a single gene in a given chromosome may occur (*e.g.*, in *Drosophila*) and that one of these variants may in turn be modified gradationally by a series of secondary factors located in other chromosomes suggests the type of organization just discussed.

With the remarkable and abundant evidence of hand-and-glove relationships between unit-characters and chromosomes that has been accumulated in recent years through the painstaking studies of workers on *Drosophila*, not to mention other corroborative work, it seems to me that there is no longer a reasonable doubt that the differentials, whatever they may be, responsible for the distinctiveness of the so-called unit-characters, reside in the chromosomes. And while I have always believed[11] and still believe that for the final outcome the cytoplasm is just as necessary in its way, and must be just as characteristic of the species as the chromosomes are, its distinctiveness must be of a fundamental organismic (probably chemical) type common to the species as a whole, since it can be, in fact is, contributed in reproduction almost wholly by one parent, the female. It is apparently a medium which responds specifically to the action of the respective chromosomal incitants, whether these be of maternal or paternal origin. All geneticists agree to-day, I think, that any character of an adult can not be merely the outcome of a unitary germinal antecedent; it is the product of many factors. And ordinarily what we see as a character-difference is probably merely the outcome of a factor-difference in one of the chromosomal cooperants.

---

[11] Bull. No. 2, Univ. of Cincinnati, Vol. III, Ser. II, 1902. *Science*, June 28, 1907. Univ. Cincinnati Studies, Sept.–Oct., 1909. AMER. NAT., XLV, 1911.

In conclusion, let me say first of all that no one more than myself realizes the inadequacy of my present argument as a complete or satisfying theory. The knowledge in the fields on which it is based is as yet far too fragmentary to warrant anything but tentative conclusions. But since various facts seem to me to point toward the view that certain types of immunological reactions, notably the cytolytic, engendered against various somatic constituents may occasionally also affect chemically related substances in the germ, and inasmuch as many other facts lend themselves to such an interpretation without undue violence to scientific credulity, I have felt justified in presenting the whole matter in the form of a working hypothesis.

In the short time remaining I can not enter into the important question of whether or not changes induced in the blood-serum might be instrumental in leading to progressive rather than regressive evolution, and even had I time for such a discussion, there are not sufficient data available to support such a discussion affirmatively. I should like merely to point out in closing that through exercise we can initiate and promote growth in various parts of the soma, we can induce hypertrophy, and in so doing we are in some way leading the protein and other constituents of the cells in question to make more of their own kind of substance, in other words, to reproduce their kind. We do not know what stimulates them to do so, but, in part, it may well be something that is or can be transported in the circulating fluids of the body; and if so, then there exists the possibility that the corresponding germinal representative of such a part, however tenuous the thread of chemical connection, might also be modified in the direction of progressive germinal change.